MOUSE MUTAGENESIS AND PHENOTYPING: DEVELOPMENTAL DEFECTS

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RFA: HD-99-007

P.T.

National Institute of Child Health and Human Development
National Institute of General Medical Sciences
National Institute on Aging
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Dental and Craniofacial Research
National Institute of Diabetes, Digestive and Kidney Diseases
National Heart Lung and Blood Institute

Public Briefing Date: June 21, 1999
Letter of Intent Receipt Date: August 2, 1999
Application Receipt Date: October 14, 1999

PURPOSE

This Request for Applications (RFA) solicits applications to establish a facility for large-scale mutagenesis and phenotyping of developmental defects in the laboratory mouse. The immediate objective of the facility is to produce and characterize mouse strains harboring mutations that affect normal developmental processes. Ultimately, the mutant mice produced in this facility are expected to help elucidate the basic cellular, molecular, and genetic mechanisms that direct embryonic and post-embryonic growth and function, as well as yield insights into the mechanisms of human disease. It is anticipated that this facility will devise and perform efficient genome wide mutagenesis, devise and perform high-throughput phenotyping to screen for mutations that disrupt normal developmental processes, and devise and perform detailed characterization of mutants that display defects in development. Mutant mice, protocols, assays, assessment criteria, and other materials and information generated in projects funded under this RFA will be made available to the wider biomedical community. The activities of this facility will be coordinated with the facility(s) established in response to RFA MH-99-007, "Mouse Mutagenesis and Phenotyping:

Nervous System and Behavior," available at http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-99-007.html, and with future, related facilities. Further information about NIH initiatives on mouse genomics and genetics resources are available at http://www.nih.gov/science/mouse.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objective of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Mouse Mutagenesis and Phenotyping: Developmental Defects, is related to several priority areas. Potential applicants may obtain a copy of "Healthy People 2000" at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications will not be accepted from foreign institutions. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators (PIs).

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) cooperative agreement (U01) award mechanism, because substantial scientific and/or programmatic interaction between institute staff and the awardee is anticipated. The cooperative agreement is used when participation by NIH staff is warranted to support and/or stimulate the recipients' activities by working jointly with the award recipients as a partner. However, NIH staff will not assume prime responsibility or take a dominant role in the activity. Details of the responsibilities, relationships, and governance of the studies funded under cooperative agreements are discussed below in "Terms and Conditions of Award" under SPECIAL REQUIREMENTS FOR COOPERATIVE AGREEMENTS.

The total project period for an application submitted in response to this RFA may not exceed five years. This RFA is a one-time solicitation. The earliest anticipated award date is August 1, 2000.

Applications received in response to this solicitation will be assigned to NICHD.

However, because this mutagenesis and phenotyping facility is of interest to all of the institutes listed as sponsors of this RFA, a resulting grant will be co-funded by all of the participating institutes. The award will be issued and administered by the NICHD.

FUNDS AVAILABLE

It is anticipated that up to $2.8 million total costs (including facilities and administrative costs) will be available for this initiative in Fiscal Year 2000, during which it is anticipated that one award will be made. An award pursuant to this RFA is contingent upon the availability of funds and the receipt of applications of outstanding scientific and technical merit.

RESEARCH OBJECTIVES

Background

The background for this initiative is detailed in a recent article entitled "An action plan for mouse genomics" (Battey, J. et al. Nature Genetics 21:73, 1999; http://www.nih.gov/science/mouse/reports/actionplan.html). Briefly, in 1998, a meeting was convened by the NIH to bring together a large group of distinguished scientists to make recommendations regarding priorities for generating mouse genetic and genomic resources. Resource needs in four areas were identified: structural analysis of the mouse genome, functional analysis of the mouse genome, methods and facilities for storing and distributing interesting mouse strains; and training in mouse pathobiology. The full report of this meeting can be obtained from the NIH web site (http://www.nih.gov/welcome/director/reports/mgenome.htm).

Mutant mouse strains provide new and critical insights into the molecular mechanisms governing normal and disrupted biological processes. Two centers outside the U.S. are currently aimed at increasing the number of mutant strains by mutagenesis using N-ethyl-N-nitrosourea followed by phenotyping: the MRC Mammalian Genetics Unit, Harwell, UK (http://www.mgc.har.mrc.ac.uk/mutabase/) and the ENU-Mouse Mutagenesis Screen Project, Neuherberg, Germany (http://www.gsf.de/isg/groups/enu/enu_cpt.html). The current RFA is being issued to respond to the need of the biological community for additional mouse strains with which to perform functional analysis of the mouse genome, with a particular focus on genes that affect embryonic and post-embryonic development. A companion RFA (MH-99-007) is focused on genes that affect the nervous system and behavior.

Scope and Objectives

This RFA will establish one facility that will perform large-scale, whole-genome mutagenesis and phenotyping of mouse strains of utility for understanding embryonic and post-embryonic development. These mutant animals, along with their embryos and/or sperm, will be made available for wide distribution to the scientific community. In particular, the facility will be required to:

o Perform efficient genome-wide mutagenesis to produce mutants with developmental defects. The strategy must enable identification of both dominant and recessive mutations.

o Perform an initial, high throughput phenotypic screen to identify and summarize the general features of mutants with developmental defects.

o Perform a focused phenotypic characterization of the genetic and biological features of those mutants that display defects in development (see examples, below). Characterization may include examination of the mutant's developmental, anatomical, cellular, physiological, molecular, genetic, metabolic, and pathological features.

o Develop and maintain a database including all of the phenotypic data on these mutant mice.

o Describe a plan to permit guest investigators, not associated with the proposed facility, to make use of the facilities to screen for, and/or to examine, developmental defects that are not the facility's primary focus. Funding for such additional projects would come from other sources.

o Develop two plans to make these mice available to the scientific community. The first plan should describe how the mutants could be housed at, and distributed directly from, the facility (either within the original budget or with supplemental funds that may be made available in the future). The second plan should describe how the mutants could be sent to the National Center for Research Resources (NCRR)-sponsored Mutant Mouse Regional Resource Center (see RFA RR-99-001, http://grants.nih.gov/grants/guide/rfa-files/RFA-RR-99-001.html) from which they will be distributed. The actual means of distribution will be determined after the award is made.

o Develop a plan to ensure that the mice, and their embryos and/or sperm, that will be distributed are free from pathogens.

o Propose a sharing plan to insure that animals, preserved embryos/sperm, phenotyping assays, and phenotypic data for all mutant strains are widely available to the scientific community. Requirements for distribution of biomaterials and data are outlined below in Dissemination of Research Resources under OTHER SPECIAL REQUIREMENTS.

o NIH expects to make a Determination of Exceptional Circumstances (DEC) to eliminate the potential for patents on mutant mice, embryos, and sperm. The application should include a proposed plan addressing if, or how, the PI and recipient institution will exercise their intellectual property rights regarding other patentable research resources not covered under the DEC, such as mutagenesis protocols, instrumentation, and phenotyping assays produced in projects funded under this RFA (these issues are addressed below under OTHER SPECIAL REQUIREMENTS).

Investigators should devise and perform an initial screen and a focused characterization that is capable of identifying multiple broad domains of development. These screens will include a variety of assays that measure multiple components of development, physiology, and cellular function. These phenotypes may include, but are not limited to, the following:

o Defects leading to embryonic lethality;

o Patterning defects, such as alterations in the basic body plan, or absence or duplication of structures;

o Alterations in organogenesis;

o Alterations in growth rate, or life span;

o Defects that may alter reproductive function;
o Alterations in cell cycle control or apoptosis;

o Alterations in responses to biological and environmental stress, such as oxidative damage, extreme temperature, or radiation;

o Defects in homeostatic regulation, such as hypertension, glucose metabolism, abnormalities of calcium or phosphate homeostasis, aberrant mineralization of the skeleton, or imbalance in bone remodeling.

SPECIAL REQUIREMENTS FOR COOPERATIVE AGREEMENTS

Definitions

ARBITRATION PANEL: A panel that would be formed to arbitrate scientific or programmatic disagreement, should any arise, between award recipients and NIH within the scope of the award.

Awardee: The institution to which a cooperative agreement is awarded.

Cooperative agreement (U01): An assistance mechanism in which there is anticipated substantial programmatic involvement by NIH staff with the recipient organization during the performance of the planned activities.

Principal Investigator (PI): The researcher who assembles the project, is responsible for submitting the application in response to this RFA, and is responsible for the performance of the project. The PI will coordinate project activities scientifically and administratively.

NIH Program Director: A scientist of the NIH program staff who represents the funding institutes on the External Advisory Committee and coordinates the activities of the facility based on his/her knowledge of other, related NIH-supported research and resource activities.

External Steering Committee (ESC): The facility's main governing committee, and the committee through which the NIH interacts and collaborates with the facility. The ESC consists of the facility's PI, 1 or 2 NIH Program Directors, and three additional scientists (advisors) not affiliated with NIH or the facility.

Mouse Genomics and Genetics Scientific Panel (MSP): The committee that provides the NIH with advice on integrating and coordinating the facility funded under this RFA with the facilities funded by MH-99-007, and with other related facilities. It consists of about 10 scientists who are not affiliated with any of the facilities. The members will be appointed by the NIH.

II. Terms and Conditions of Award

The following Terms and Conditions will be incorporated into the award statement.
They are to be followed in addition to, and not in lieu of, otherwise applicable
OMB administrative guidelines, HHS grant administration regulations at 45 CFR

Parts 74 and 92 (Part 92 is applicable when state and local governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

1. The administrative and funding instrument used for this program will be the U01, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH scientific and/or programmatic involvement with the PI is anticipated during performance of the activities. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the PI's activities by involvement in and otherwise working jointly with the PI in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the PI for the project as a whole, although specific tasks and activities may be shared between the awardee and NIH program staff.

PI Rights and Responsibilities

The PI will coordinate project activities scientifically and administratively at the awardee institution and at other sites that may be supported by subcontracts to this award. The PI will have the primary responsibility for defining the details for the project within the guidelines of this RFA, and for performing the scientific activities. The PI will agree to accept close coordination, cooperation, and participation of the Program Director, the External Steering Committee (ESC) and the Mouse Genomics and Genetics Scientific Panel (MSP) in those aspects of scientific and technical management of the project described under "Program Director Responsibilities," "ESC Function," and "MSP Function" (below). Specifically, the PI will:

o Determine experimental approaches, design protocols, direct experiments, and set project milestones, in consultation with NIH program staff and the ESC;

o Release data and publish results, as agreed upon by NIH program staff and the ESC;

o Submit periodic progress reports in a standard format, as agreed upon by the ESC;

o Accept and implement the common guidelines and procedures approved by the ESC and the MSP;

o Share with other mutagenesis and phenotyping facilities mutants that may be of interest to those facilities, as directed by the ESC and the MSP;

o Be aware of mutants that the other mutagenesis and phenotyping facilities are producing, and be prepared to accept them for initial screening and/or focused characterization, as directed by the ESC and the MSP;

o Solicit the views of the broad biomedical research community for the phenotypes and/or genotypes of interest;

o Participate in ESC meetings. Budget requests should include travel funds for the PI and other critical staff to attend the ESC meetings in the Bethesda, MD area at least twice per year.

NIH Program Director Responsibilities

The Program Director(s) has substantial scientific/programming involvement that includes facilitating the partnership between NIH and the developmental defects mutagenesis and phenotyping facility, helping to balance the facility's activities with new and emerging research opportunities, and ensuring that the facility's activities are consistent with the missions of the participating institutes. They will help to maintain scientific balance between accomplishing goals and addressing emerging research opportunities. The role of NIH Program Director will be to facilitate, but not to direct activities. It is anticipated that decisions will be reached by consensus with the PI through the ESC. One or two Program Directors will participate as members of the ESC. NIH staff will have a total of one vote. NIH Program Director will:

o Provide relevant expertise and overall knowledge;

o Participate with other ESC members in the group process of setting research priorities, deciding optimal research approaches and protocol designs, and contributing to the adjustment of research protocols or approaches as warranted. The Program Director(s) will assist and facilitate the group process and not direct it;

o Serve as liaison to MSP; attend MSP meetings as a non-voting member, to help coordinate the activities of the facility with those of other NIH mutagenesis and phenotyping facilities, such as those funded under RFA MH-99-007, and with other NIH mouse genomics and genetics initiatives. The Program Director will also coordinate the activities of facilities funded under this RFA with other US and international efforts;

o Provide information about ongoing NIH-supported research and resource collections;

o Appoint the Chair of the ESC based on a recommendation from the committee's members;

o Attend ESC meetings as one voting member, and help develop operating guidelines, quality control procedures, and consistent policies for dealing with situations that require coordinated action. The Program Director(s) must be informed of all major interactions of ESC members. The Program Director(s) will be responsible for preparing, within 30 days, a concise (3 þ 4 page) summary of each ESC meeting;

o Serve as liaison between the grantee and the other NIH program staff;

o Assist in promoting the mutagenesis facility to the scientific community at large;

o Help determine the most appropriate mechanisms for release of biomaterials and data to the community, i.e., distribution by the mutagenesis facility or by other federally-funded repositories or national research resource centers;

o Coordinate the facility's activities with NIH-funded repositories and databases, to ensure the rapid and efficient distribution and long-term storage of biomaterials and data;

o Assist in developing timetables for, and facilitating, the timely and wide distribution of biomaterials and data to the biomedical community;

o Participate in data analysis, interpretations and, where warranted, co-author publications that report results of studies performed under this RFA.

4. Collaborative Responsibilities - ESC Functions

The ESC will be the main governing body of the facility for mutagenesis and phenotyping of developmental defects in the mouse. The NIH will interact and collaborate with the facility through the ESC. The ESC will include the PI of the facility, one or two Program Directors, and three additional scientists (advisors) whose expertise is required for breadth and balance. These advisors will be appointed by the NIH. The NIH Program Director(s), the PI, and each advisor will have one vote. One of the unaffiliated advisors will be appointed to be the committee's chair by the Program Director, in consultation with ESC members. The chair will schedule the first meeting, and will be responsible for developing meeting agendas and chairing the meetings. The ESC will meet at least twice per year. A schedule for subsequent meetings will be prepared at the first meeting. Additional ESC members may be added by an action of the original ESC

members. Other NIH staff may attend the ESC meetings, as their expertise is required for specific discussions.

The ESC will coordinate the facility's activities, and the exchange of information and biological materials with the scientific community. They will discuss scientific goals and progress, make recommendations regarding how mutations could be obtained, analyzed, and collected in order to be maximally valuable to all interested investigators. Even though mutagenesis of multiple regions of varying size across the whole genome will be conducted, it is expected that the ESC will establish priorities for genomic regions and for phenotypes of particular interest. The ESC will address the recommendations made by MSP. The PI should request funds in the budget to attend the ESC meetings in the Bethesda, MD area at least twice per year.

MSP Functions

MSP will coordinate activities among the facilities and resources participating in NIH's mouse mutagenesis and phenotyping initiative, including this RFA and RFA MH-99-007. MSP will use its knowledge of the activities of all of the participating facilities to ensure adequate investigation, communication and sharing, and to avoid redundant activities. It will advise NIH with respect to the coordination of all activities that involve the mutagenesis, phenotyping, maintenance, and distribution of mutant mouse strains. The MSP will evaluate and make recommendations regarding the coordination of the activities of the facilities that are funded by the mutagenesis and phenotyping initiatives, and other related activities that may be developed in the future.

It will be the responsibility of the MSP to make recommendations that will lead to exchanging mutants among the facilities, sharing assay strategies, adopting common policies on data sharing, creating compatible databases, and other activities that will make these facilities of maximal utility to the scientific community. The MSP will also set standards for data format and nomenclature, as well as develop common guidelines and procedures for deposition of the primary phenotypic data, and for the preservation of mutant mouse strains.

The committee will consist of about 10 scientists (advisors) who are not affiliated with any of the mutagenesis and phenotyping facilities, and are not members of the advisory committees of those facilities. They will be appointed by the NIH. These advisors will be selected for their broad expertise in relevant topics such as developmental biology, neurobiology, behavior, mutagenesis, phenotyping, mouse genetics, husbandry, genomics, and database issues. The MSP will meet at least once each year. A schedule for subsequent meetings will be prepared at the first meeting.

The NIH will select one member to be the committee chair, after considering MSP's recommendations. The chair will schedule the first meeting, and will be responsible for developing meeting agendas and chairing the meetings. Additional MSP members may be added by an action of the original MSP members. The NIH Program Director(s) will attend MSP as non-voting members and will act a representative of ESC. Other NIH staff and ESC members may attend MSP meetings, when their expertise is required for specific discussions.

Milestones and Evaluations

Applications should define yearly milestones, which may be modified at the time of the award. The awardee's milestones will be provided to the ESC. It is expected that the milestones should be adjusted annually at the award anniversary dates, both to incorporate the group's scientific accomplishments and progress in the field in general, as well as to reflect the recommendations of the ESC and the MSP. In accordance with the procedure described above, NIH program staff may recommend augmenting any project, as discussed with the ESC, or reducing or withholding funds if the project substantially fails to meet its milestones or to remain state-of-the-art.

7. Arbitration Process

Any disagreements that may arise in scientific or programmatic matters within the scope of the award between grantees and the NIH may be brought to arbitration. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulations 42 CFR Part 50, Subpart D, and HHS regulation at 45 CFR Part 16. An Arbitration Panel will help resolve both scientific and programmatic issues that develop during the course of work that restrict progress. The Arbitration Panel will be composed of three members: a designee of the ESC chosen without the NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two members.

OTHER SPECIAL REQUIREMENTS

Restricted availability of unique research resources, upon which further studies are dependent, can impede the advancement of research and delivery of medical care. The sharing of biomaterials, data, and software in a timely manner, on the other hand, has been an essential element in the rapid progress that has been made in the genetic analysis of mammalian genomes. NIH policy requires that investigators make unique research resources readily

available for research purposes to qualified individuals within the scientific community when they have been published (NIH Grants Policy Statement may be found at http://grants.nih.gov/grants/policy/nihgps/). Biomaterials (pathogen-free mutant animals, preserved embryos and sperm) and other patentable research resources e.g., phenotyping assays, protocols, instrumentation) produced in projects funded by this RFA will be made available and distributed to the broader scientific community.

For applications submitted in response to this RFA, three special requirements exist regarding research resources produced in the proposed project: (1) applicants are required to include a specific plan by which they will share research resources with the wider scientific community; (2) NIH expects to make a Determination of Exceptional Circumstances (DEC) to eliminate the potential for patents on mutant mice, embryos, and sperm; and (3) applicants are required to include a plan addressing if, and how, they will exercise their intellectual property rights while making available to the broader scientific community other patentable research resources (e.g., phenotyping assays, protocols, instrumentation, and methodologies) not covered under the DEC. Each is discussed in detail below.

Plan to Share Research Resources

To address the joint interests of the government in the availability of, and access to, the results of publicly funded research, NIH requires applicants who respond to this RFA to propose detailed plans for sharing the research resources generated through the grant. It is expected that the resources to be shared include all materials developed in projects funded under the RFA, including but not limited to, the following: mutant animals, preserved embryos and sperm, phenotypic and genetic data, phenotyping assays, instrumentation, and mutagenesis protocols. For this purpose, it is the view of NIH that dissemination of such data and materials via individual laboratories and Web sites is not sufficient, as it would force interested investigators to search several different data collections to make use of the results of this initiative. It is preferable that data, protocols, technologies, and biomaterials generated in grants funded under this RFA should be placed in common, public repositories and databases that are widely accessible by investigators in the scientific community.

It is expected that the investigator's data and biomaterials sharing plan will include the following elements: (1) establishment of and access to a comprehensive database containing detailed results from phenotyping screens; (2) access to mutants identified through high-throughput phenotyping; (3) access to preserved embryos and/or sperm for these mutants; (4) access to phenotyping assays not currently available to the wider scientific community that are used to

characterize mutants; (5) access to mutants that have been screened and found to have phenotypes that are not of interest to investigators associated with this facility. This means that, before discarding rejected mice, the facility will specifically advertise their availability to the facility supported under RFA MH- 99-007, and other investigators in the wider scientific research community wishing to conduct screens of their own, but who do not otherwise have access to mutagenesis facilities. If demand for these mice is great enough, the facility may have to develop priorities and rules for distribution; (6) elaboration of mechanisms and protocols to be followed to promote the wide distribution of resources to investigators in the scientific community; and (7) a distribution timeline.

The scientific review group will evaluate the adequacy of the proposed plan for sharing and data access. The adequacy of the plan also will be considered by NIH program staff in determining whether the grant shall be awarded. The sharing plan as approved, after negotiation with the applicant when necessary, will be a condition of the award. Evaluation of any future renewal applications will include assessment of the effectiveness of research resource release.

It is expected that this plan will include all elements of the guidelines developed by the NIH and the Department of Energy (DOE) to address the special needs of genome research. These guidelines call for material and information from genome research to be made available within six months of the time the data or materials are collected, and are available at http://www.nhgri.nih.gov/Grant_info/Funding/Statements/data_release.html.
Adherence with this time frame is highly desirable. More rapid sharing is encouraged. Requests for exemptions or extensions will require compelling justification and will be fully evaluated through peer review and by NIH program staff.

Where appropriate, the awardee may work with the private sector to make unique resources available to the wider biomedical research community at a reasonable cost. Applicants may request funds to defray the costs of sharing resources, with adequate justification.

Intellectual Property Rights

NIH is interested in ensuring that the research resources developed through this RFA become readily available to the research community. To ensure unrestricted availability of mutant mice developed under this RFA, NIH expects to make a Determination of Exceptional Circumstances (DEC) pursuant to 37 C.F.R. 401.3(a)(2) which will cover mutant animals, embryos, and sperm. The purpose of the DEC is to eliminate the potential for patents on mutant mice, embryos, and

sperm to undermine the development of a widely available national resource that is the fundamental purpose of this RFA.

With regard to other patentable research results, such as mutagenesis strategies, phenotyping assays, protocols, instrumentation, and methodologies, NIH requires applicants who respond to this RFA to develop and propose a plan addressing if, and how, they will exercise their intellectual property rights while making available to the broader scientific community research resources produced in projects funded under this RFA. This is expected to include an elaboration of the applicant's anticipated plans to generate, or not generate, patents and/or exclusive or non-exclusive licensing of biomaterials and other patentable subject matter created in projects funded under this RFA. This plan is also expected to include disclosure of any pre-existing intellectual property rights, including options to for-profit research sponsors, that are associated with biomaterials and data that may be generated. Note that this plan will NOT include mutant animals, embryos and sperm (for which the potential for patents will be eliminated pursuant to the DEC described above). This plan is in addition to the plan for sharing and disseminating research resources described in the previous section.

The scientific review group will evaluate the proposed plan. The plan also will be considered by NIH program staff in determining whether the grant shall be awarded. The plan as approved, after negotiation with the applicant when necessary, will be a condition of the award. Evaluation of any future renewal applications will include assessment of the awardee's adherence to the proposed plan.

Applicants are also reminded that the grantee institution is required to disclose each subject invention to NIH within two months after the inventor discloses it in writing to grantee institution personnel responsible for patent matters. The NICHD reserves the right to monitor awardee activity in this area to ascertain if patents or patent applications on phenotyping assays, protocols, instrumentation, methodologies or other patentable subject matter are adversely affecting the goals of this RFA.

PUBLIC BRIEFING

Prospective applicants are invited to attend a public briefing on the facility for mutagenesis and phenotyping of developmental defects and the related facility for mutagenesis and phenotyping of the nervous system and behavior (RFA: MH-99- 007) on June 21, 1999 at the NIH Campus in Bethesda, MD. NIH staff will explain the purpose of these RFAs, provide instructions regarding the application and review processes, and answer questions. Potential applicant institutions are

urged to send a representative to this briefing, both to gather information and to exchange ideas with other potential applicants. Anyone who cannot attend the pre-application meeting may obtain any distributed materials and a summary of the discussion. For further information about this meeting, please contact the NICHD Program Staff listed under INQUIRIES.

LETTER OF INTENT

Prospective applicants are asked to submit, by August 2, 1999, a letter of intent that includes a descriptive title of the proposed research, the name, address, telephone and facsimile numbers, and the E-mail address of the PI, the identities of other key personnel and participating institutions, and the number and title of this RFA. Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information it contains will allow NIH staff to estimate the potential review workload and avoid conflicts of interest in the review.

The letter of intent is to be sent to:

Dr. Steven Klein
Developmental Biology, Genetics and Teratology Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 4B01
Rockville, MD 20852
Telephone: (301) 496-5541
FAX: (301) 480-0303
Email: KleinS@Exchange.NIH.GOV

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for this grant. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, Email: grantsinfo@nih.gov. It is also available at http://grants.nih.gov/grants/funding/phs398/phs398.html.

Because the application is expected to be more complex than applications for regular research projects, the Research Plan section may be up to 40 pages in length. Within this page limitation,

the application should include separate sections on 1) overall strategy, purpose and plans, 2) mutagenesis (including breeding strategy), 3) phenotyping, 4) database/bioinformatics, and 5) procedures for distribution and sharing. For the purpose of accomplishing the goals of this RFA, the facility may include investigators at more than one site, and subcontracts may be included in the budget to support investigators at sites other than the awardee institution. Applications should define yearly milestones, which may be modified at the time of award. Budget requests should include travel funds for the PI and other critical staff to attend the ESC meetings in the Bethesda, MD area at least twice per year.

The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number, "Mouse Mutagenesis and Phenotyping: Developmental Defects: HD-99-007," must be typed on line 2 of the face page of the application form, and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and four signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, send one additional copy of the application to:

Dr. Steven Klein
Developmental Biology, Genetics and Teratology Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 4B01
Rockville, MD 20852
Telephone: (301) 496-5541
FAX: (301) 480-0303
Email: KleinS@Exchange.NIH.GOV

Applications must be received by October 14, 1999. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR, and for responsiveness by the staff of the participating institutes. Incomplete and/or nonresponsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to this RFA will be evaluated for scientific and technical merit in accordance with the criteria stated below by an appropriate peer review group convened by CSR, in accordance with the review criteria stated below. These reviews will not include site visits. As part of the initial merit review, a process will be used by the scientific review group in which applications receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score. Scored applications will receive a second level of review by the National Advisory Child Health and Human Development Council, the National Advisory General Medical Sciences Council, the National Advisory Council on Aging, the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council, the National Advisory Dental and Craniofacial Research Council, the National Diabetes and Digestive and Kidney Diseases Advisory Council, and the National Heart Lung and Blood Advisory Council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority

score. For example, an investigator may propose to carry out important work that by its nature is not innovative, but is essential to move a field forward.

o Significance: What will be the expected impact of the mutant mice produced by the facility on our understanding of the genetic bases of development? Will the facility have the capacity to serve as a resource for the wider scientific community?

o Approach: Does this study specify methodologies for rapid and efficient genome-wide mutagenesis and high-throughput phenotypic characterization? Is the conceptual framework for efficiently conducting large-scale mutagenesis across the mouse genome and for comprehensive high-throughput phenotyping, adequately developed, well integrated, and appropriate to the aims of the project? Will the proposed strategy enable identification of both dominant and recessive mutations that alter developmental processes? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the Principal Investigator and other researchers (if any)?

o Integration with other resources: Are the plans adequate to integrate the mutants and the phenotypic data with those collected in other comparable projects? Are the plans adequate to ensure that mutants that may be of interest to the other mutagenesis and phenotyping facilities will be shared those facilities? Are the plans adequate to ensure that the facility will be aware of mutants produced by the other mutagenesis and phenotyping facilities, and that they will be prepared to accept them for examination?

o Exportability and accessibility: What is the likelihood that the mutants and phenotypic information generated in the project will be made widely available in a timely fashion to the scientific community? Are state-of-the-art procedures employed to ensure the distribution of pathogen-free mutant strains, embryos, and/or sperm? What is the likelihood that other patentable methodologies and research results will be widely available for the scientific community, given the proposed plan to exercise, or not to exercise, intellectual property rights regarding these methodologies and results? Does the project specify plans for creation of a

highly efficient and organized bioinformatics database? Do the investigator's quality control plans assure that databases provided to the wider scientific community will be accurate and highly efficient?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

Reviewers will also evaluate:

o the response to the Research Objectives described above;

o the ability of the project to establish an infrastructure that will permit rapid and efficient achievement of the project aims;

o the proposed project's ability to serve as a resource to the broader scientific community;

o the plan to share research resources and the plan to exercise (or not exercise) intellectual property rights regarding patentable research resources (e.g., mutagenesis protocols, phenotyping assays, instrumentation, and methodologies) not covered under the DEC;

o the adequacy of plans for participation by guest investigators;

o the safety of the research environment.

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

AWARD CRITERIA

The earliest anticipated date of award is August 1, 2000. Subject to the availability of funds, and consonant with the priorities of this RFA, NICHD, NIGMS, NIA, NIAMS, NIDCR, NIDDK, and NHLBI will provide funds for a project period not to exceed five years. Factors that will be used to make award decisions are as follows:

o Scientific and technical merit of the proposed project as determined by rigorous scientific peer review;

o Cost effectiveness of the proposed strategy;

o Promise of the proposed project to accomplish the goals of this RFA, including the performance of rapid, cost-effective high-throughput mutagenesis and phenotyping;

o Availability of funds.

SCHEDULE

Public Briefing Date: June 21, 1999
Letter of Intent Receipt Date: August 2, 1999
Application Receipt Date: October 14, 1999
Peer Review Date: February/March 2000
Advisory Council Date: May/June 2000
Earliest Award Date: August 1, 2000

INQUIRIES

Inquiries concerning this RFA are strongly encouraged. NIH staff welcome the opportunity to clarify issues or questions from potential applicants. Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.865 (NICHD); 93.862 (NIGMS); 93.866 (NIA); 93.846 (NIAMS); 93.121 (NIDCR); 93.849 (NIDDK); and 93.838 (NHLBI). Awards are made under authorization of the Public Health Service Act, Title IV, Part A

(Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards will be administered under PHS grants policy as stated in the NIH Grants Policy Statement (October 1, 1998).

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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